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A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA.(U)
JAN 77 F D MOORE, N E O'CONNOR DADA17-73-C-3022

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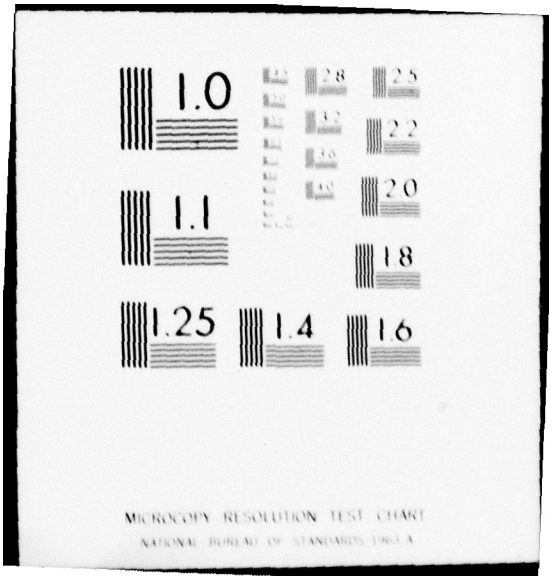
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REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: 1
2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle): A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA.

5. TYPE OF REPORT & PERIOD COVERED: Annual Summary Report, no. 1, ~~Feb. 1, 1976-Jan. 31, 1977~~ 1 Feb 76 - 31 Jan 77

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s): Francis D. Moore ~~and~~ Nicholas E. O'Connor

8. CONTRACT OR GRANT NUMBER(s): DADA 17-73-C-3022

9. PERFORMING ORGANIZATION NAME AND ADDRESS: Department of Surgery of Harvard Medical School at the ~~Peter Bent~~ Brigham Hospital 721 Huntington Ave., Boston, Mass. 02115

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 31 Jan 77

11. CONTROLLING OFFICE NAME AND ADDRESS: U.S. Army Medical Research and Development Command, Washington, D.C. 20314

12. REPORT DATE: Feb. 1, 1976-Jan. 31, 1977

13. NUMBER OF PAGES: 8

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office): 11 p.

15. SECURITY CLASS. (of this report): unclassified

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release, distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Amino Acids	Ketone	Catheter
Glucose	Nitrogen Balance	Bacterial Endocarditis
Glycerol	Free Fatty Acid	Airway Closure
Glucagon	Tritiated Glucose	Pulmonary Extravascular water
Fat Emulsion	Carbohydrate	

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Studies were performed showing that amino acid infusion alone does not result in a favorable protein economy in starving, resting man. Addition of ~~1)~~ carbohydrate at two dose levels, ~~2)~~ glycerol, or ~~3)~~ triglycerides to the amino acid infusion will all markedly improve nitrogen balance.

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unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

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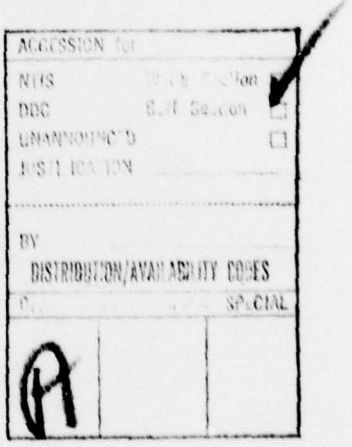
20. ABSTRACT (continued)

Studies in animals demonstrated an association between pulmonary engorgement and edema and small airway closure. Positive-end expiratory pressure reduced the volume of trapped gas but did not abolish edema formation.



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REPORT #1

"A Program for Clinical Care in Physical Trauma"

ANNUAL SUMMARY REPORT

Francis D. Moore, M.D.

and

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February 1, 1976-January 31, 1977

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Washington, D.C. 20314

Contract No. DADA 17-73-C-3022

Department of Surgery

of

Harvard Medical School

Peter Bent Brigham Hospital

Boston, Massachusetts 02115

PROGRESS REPORT - February 1, 1976 - January 31, 1977

The Metabolic Basis of Intravenous Feeding in Traumatized Patients

I SUBSTRATE INTERACTION - GLUCOSE, AMINO ACIDS, GLYCEROL AND FAT

1. Maximum Glucose Intake In Fasting Man

In prior experiments reported several years ago (O'Connell), we found that in normal fasting man the basal nitrogen excretion could be lowered to a minimum or floor level by glucose infusions at the approximate intake of 750 grams per day. The nitrogen sparing effect of carbohydrate was spectacular but there seemed to be a maximum achievable sparing effect at that level of intake. In the current experiments it was our object to determine if nitrogen excretion could be reduced to an even lower level by increasing glucose intake to excessively high values. As will be noted, the experiments had to be terminated because of symptomatology on the part of the subjects, a most interesting finding in itself. Specifically, our object with the glucose infusions was to increase the intake to approximately 1000 grams of glucose a day. In two successive subjects, the observations had to be stopped because of unusual signs and discomfort on the part of the recipient including right upper quadrant pain and a rise in liver enzymes. There was little overt sign of serious disorder upon physical examination but the subjects felt very uncomfortable and complained of headache. Blood chemical changes showed some elevation of glucose to a greater extent than was seen at the lower levels of intake. Hormone and amino acid results have not yet been returned; the experiments were discontinued.

These experiments teach an important lesson: that carbohydrate (as well as fat) given in excess of caloric requirements can produce unfavorable reactions that appear to be localized in the liver. It will be recalled that about 1960, in experiments conducted under Army sponsorship and in part at the Walter Reed Army Institute of Research, it was demonstrated that when Lipomul (a coconut oil fat emulsion then available and widely used) was infused intravenously in amounts grossly in excess of caloric requirements, there was severe subjective symptoms including fever and in some, instances of severe liver damage.

This demonstration of an analogous response with excessive glucose intravenous infusions, while only a small part of our work this past year, will be reported in the literature separately, because it serves as a warning, in the present period of enthusiasm for mixed high caloric intravenous feedings, that one must beware of providing caloric intakes grossly in excess of physiologic requirements, even though the components are entirely nonlipid in character.

2. Amino Acids As The Sole Substrate For Intravenous Provision In Normal Fasting Man

These experiments have been completed and mark the major achievement of 1976. The analyses of amino acid levels have all been completed and returned. A manuscript has been accepted for publication in the Annals of Surgery and will appear within the next month or two. It appears

to us that this is the most important contribution from our laboratory since the glucose and nitrogen sparing paper referred to in the preceding paragraph.

The findings are of remarkable interest because they demonstrate for the first time, clearly and in man, that amino acids given alone in a quantity of approximating 90 grams per day (nitrogen intakes about 6 gms/M^2/d) does not result in a favorable protein economy. In normal fasting human subjects it instead produces a negative nitrogen balance. These are the most favorable possible circumstances for improving nitrogen economy and it is a remarkable finding that amino acids alone are unable to support the body cell mass. These experiments were carried out in four subjects hospitalized and cared for using the highly specialized protocol referred to in last year's application. The periods of study approximate eight days in length and were long enough to permit full equilibration and provide entirely adequate interprative basis.

Despite a progressive ketosis there was no improvement in nitrogen metabolism over the period of time observed. Insulin levels did not drop to starvation concentrations and glucagon rose briskly. There was evidence of conversion of essentially all of the infused material into glucose or other energy substrates, with the excretion of all the nitrogen as urea. In addition, since the patients were in a negative nitrogen balance approximating 3-4 gms/M^2/d it was clear that there was a continuing draft on the patient's endogenous protein stores to make up some biological deficit perceived by the body either in calories or specific carbon chain configurations. The amino acid preparation used was FreAmine II.

Plasma amino acid analyses have been completed and are included in the report. Most of the amino acid concentrations behaved according to the infusion gradient. Only phenylalanine and methionine showed exceptions to this rule since they both rose briskly despite the fact that they were not present at high concentrations in the infusion.

In our published report we make it clear that one cannot extrapolate from the normal human fasting volunteer to the many stressful details of the acutely traumatized patient. Nonetheless, we feel that the fasting normal human volunteer represents an optimal favorable situation for utilization of intravenous nourishments. If in such a setting one cannot achieve a favorable nitrogen economy it appears highly unlikely that the acutely or chronically traumatized or septic individual will have a favorable response. Unstressed starvation alone may improve nitrogen economy over the normal resting fast but this would not be the case with acute trauma or sepsis.

In conjunction with this work we have carried out some amino acid infusions in chronically starved surgical patients as will be mentioned below.

3. The Addition Of Carbohydrate At Two Dose Levels To The Amino Acid Infusion

These studies have likewise been completed and are being prepared for publication. They will be presented at the Spring meeting of the American Surgical Association. They involve the administration of glucose at low dose (approximately 150 grams per day) and at a high dose (approximately 750 grams per day) along with the same amino acid infusions given in precisely the same amount and composition as those mentioned above.

The effects of carbohydrate infusion on amino acid utilization and on body economy, are spectacular. At the low dose of glucose there was a marked improvement in nitrogen economy and at the higher dose a positive balance is readily achieved with the amino acid infusions which, alone, provide a negative nitrogen balance.

In the latter connection it is important to emphasize that one cannot maintain normal human subjects on a program that will produce a prolonged positive nitrogen balance, because their body size components will not permit unlimited nitrogen loading if they start at a body size that is determined by exercise and genetics. Nonetheless, normal persons can be placed in positive transient nitrogen balance as was the case here. The statistical examination of the differences with amino acids alone as compared with those using added glucose, demonstrate a clear difference at both dose levels of glucose, with a marked improvement in nitrogen economy in both.

Ketone development is inhibited immediately by any amount of glucose given. The concept that ketosis is somehow favorable to nitrogen economy finds no basis in these experiments. At the low dose of glucose, insulin concentrations are not markedly elevated but nitrogen economy is markedly improved indicating that the availability of carbon chains for oxidation apparently improves nitrogen economy even though there is low stimulation to insulin production.

At the higher glucose dosage, the hormone results are quite remarkable. Insulin is now seen to be remarkably stimulated, rising to about five times its resting value. The glucagon level is dramatically inhibited to the lowest concentrations that we have seen in this laboratory with this endocrine setting, negative nitrogen economy disappears and a strongly positive balance is produced.

It would appear to be a clear demonstration of the need for a "balanced diet" in intravenous feeding and of the fact that carbohydrate, rather than having a deleterious action, has a remarkably favorable effect on nitrogen economy in intravenous feedings.

In addition, in the study of two surgical patients both chronically starving, the same glucose effect was clearly demonstrated with a marked improvement in nitrogen economy with added carbohydrate. In one of the starving patients the utilization of amino acids alone was better than it was in the normal.

4. Glycerol and Fat

Three years ago our laboratory reported (Brennan) that an amount of glycerol equivalent to that contained in the intralipid infusion had a marked effect on protein sparing. This three carbon carbohydrate (sometimes referred to as three carbon alcohol) is added to the infusion to make it isotonic. The molecule is both lipid soluble and water soluble. On a weight-for-weight basis, it is at least equivalent to glucose in its protein sparing effect. This suggests that the glycerol component of intralipid infusions is not to be neglected in the metabolic study of intravenous fat. Intralipid infusions contain added glycerol as well as that made available by the hydrolosis of the triglycerides. Our findings did not suggest nor did we ever propose that glycerol should be used clinically. Rather, this was a research demonstration that a small molecular weight carbohydrate - alcohol with unusual water-solubility properties, could be used as an energy source. Entirely free of nitrogen and devoid of any effect of insulin or glucagon concentrations, it nonetheless had a marked effect on protein sparing in man.

We can now report that glycerol given with the amino acid infusions has the same effect. Namely, that it improves the utilization of intravenously provided amino acids just as it spares nitrogen in normal fasting man.

We have proceeded on now to the intralipid studies with amino acids and the findings are quite unexpected. From some reports in the older literature one would have predicted that fatty acid infusion would have little effect on nitrogen economy because fatty acids cannot be interconverted either into carbohydrate or into amino acids. In addition, interpretation of the intralipid experiments require the prior data on glycerol so as to control or factor out the glycerol component in the intralipid infusions.

Our findings show that the intralipid infusion has a clearly increased nitrogen sparing and protein anabolizing effect over and beyond that observed with the glycerol contained or released in the infusion. The intralipid infusion is accompanied by a very mild ketosis, mild in all likelihood because of the fact that the glycerol present inhibits ketone formation. Fatty acid levels in the plasma are of course increased and triglyceride levels are very high. There is no stimulus to an increased insulin concentration. We have here therefore an additional evidence that the provision of energy sources can stimulate and improve nitrogen economy in man without the necessary intermediacy either of glucagon inhibition or insulin stimulation.

The amino acid results from these experiments are still being analyzed and have not yet been returned.

These findings likewise provide no support for the concept that muscle anabolism is somehow conducted at the expense of synthesis of visceral or acute phase proteins.

II BRANCH CHAIN AMINO ACIDS

As indicated in the application last year we undertook the study of branch chain amino acids in animals. The human studies are supported by the public health service and will be reported elsewhere, though mentioned briefly here because of their interest in trauma metabolism.

In animals branch chain amino acids given intravenously alone do not seem to have any remarkably adverse effect from toxicity point of view save, in dogs, for a rather brisk rise in serum uric acid concentration.

Infusion used was one prepared for us by Vitrum, Inc. in Sweden. Elaborate precautions in preparations and documentation of toxicity was required for its FDA approval in this country. It is important to note that our particular intravenous solution of branch chain amino acids has received full approval by the Federal Drug Administration.

Experiments in man (supported from other research funding sources) has now been completed and demonstrates that the material does not have any remarkably adverse metabolic effect in man but does have a mild hyperurecemic effect, as well as that of acute hyperglycemia in some instances. The latter effect requires further elucidation. Infusion of the branch chain amino acids alone does not provide any remarkable stimulus to protein synthesis.

III GLUCOSE COMPOSITION STUDIES USING TRITIATED GLUCOSE

During this past year it was the special project of Dr. Peter Wright to conduct a series of experiments in which tritiated glucose was used as a tracer for glucose. Without going into details here it appears that the tritiated glucose is an almost ideal tagged entity for use in man. It has many advantages. It is easy to prepare and count. The tritium is never recycled into glucose. Once the glucose is oxidized the tritium appears in body water. By estimates of body water it is possible to estimate the total rate of glucose oxidation. Our laboratory is well set up for the radioactive measurements of tritium. The experiments can be conducted in only a few hours and the results are clearly reproducible.

They show that the glucose turnover rate (K value of percent turnover per time) as measured by the single exponential decay curve of tritium, are remarkably constant in a whole variety of circumstances. Pool sizes however vary remarkably being elevated by glucagon and by the provision of glucose and remarkably so by insulin. Therefore the absolute replacement rate (i.e. the exponential decay expressed as grams per unit time) shows marked variability. The amount of body water available for glucose solution likewise shows variability linear with the pool size.

It is notable that insulin alone of all the substances tested has an effect on the fractional turnover rate or K value and demonstrates remarkable increase in the volume of body water involved for glucose solution.

These studies have also been completed in a series of burn patients who demonstrate an increase in pool size and body water glucose space without any change in turnover rate (K).

IV BACTERIAL ENDOCARDITIS

Since its introduction in 1970, the flow-directed balloon-tipped catheter has been widely used in monitoring the circulatory hemodynamics of critically ill patients, including burn patients. A review of six consecutive burn patients who had been monitored with a pulmonary artery catheter, and who later died of their injury, showed that four of the six had aseptic right sided endocardial lesions at autopsy, and the other two had right-sided bacterial endocarditis. This review prompted a study of the development of right sided endocardial lesions in dogs with indwelling pulmonary artery catheters.

Dogs were anesthetized, No. 7 French Swan-Ganz thermodilution catheters were inserted into the external jugular vein, and directed into the pulmonary artery. The end of the catheter was cut off at the venous cutdown site, and the skin closed, so the end of the catheter was buried subcutaneously. The dogs were sacrificed at 1, 3, 5, 7, 10, 12, and 14 days following insertion and their hearts examined. All the dogs showed non-bacterial thrombotic endocardial lesions of the superior vena cava, right atrium, tricuspid valve, right ventricle, and pulmonic valve. One each of the seven and twelve day dogs developed abscesses at their venous cutdown sites and had acute bacterial endocarditis of the tricuspid and pulmonic valves. Two dogs had their catheters removed after five days and were sacrificed two weeks later. Examination of their hearts revealed endocardial lesions which were well organized with marked fibrosis.

This study demonstrates that the constant pumping action of the heart against a stiff indwelling catheter can easily traumatize the endocardium or endothelium of a vessel. The resultant thrombotic lesions can easily become infected leading to acute bacterial endocarditis. These non-bacterial lesions organize quickly and are well on their way to healing in three weeks.

V AIRWAY CLOSURE

Small airways in the lung, 2 mm. or less in diameter, are not supported by cartilage and are thus susceptible to collapse. Airway closure occurs when the compressive forces outside airways exceed intra-airway pressure. Over this past year our studies on the relationship between elevated pulmonary extravascular water in small airway closure were published. These studies demonstrated that the slow accumulation of lung water achieved by a combination of pulmonary venous hypertension and mild hemodilution was associated with an increase in trapped gas volume. The extravascular water was measured using a double indicator dilution method based on the differential right to left transit time for a simultaneously injected Evans blue dye and tritiated water. The trapped gas volume was measured by the helium equilibration technique. Clinically undetectable levels of pulmonary engorgement and edema were reproducibly associated with an increase in gas trapping. Positive-end expiratory pressure which increased the functional residual capacity, reduced the volume of trapped gas but did not abolish edema formation. Using these methods, the evaluation of airway closure with consequent gas trapping and pulmonary shunting is currently non-invasive, simple and safe. Determination of gas trapping or closing volume should be incorporated into the routine preoperative evaluation of patients prior to major surgery in an effort to determine which patients would benefit from continued ventilation with end expiratory pressures following surgery.

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